REMARKS

In the Advisory Action mailed March 10, 2004, the Examiner maintained her decision to deny entry of the Amendment proposed in Applicant's reply filed November 5, 2003 on grounds that it raises new issues that would require further consideration and/or search, and that it raises the issue of new matter. The Examiner also states that the Amendment may raise 35 U.S.C. § 112, 2nd paragraph issues (i.e., with respect to the language "antibody-component"). Applicant's Amendments filed on November 5, 2003 (other than formalities such as correction of claim dependency) solely consisted in (i) replacing the language "wherein seconds are thirds" with "wherein the second antibody is a third antibody" (language which, save the word "antibody", had been suggested by the Examiner); and (ii) replacing the language "ligand" with "antibody". The language "ligand" and the notion that the ligand may be an antibody were introduced into the claims as early as June 1, 2001 (See, for example, claim 52 on page 4 of Applicant's Response filed June 1, 2001). In addition, in their Response to Restriction Requirement filed October 10, 2002, Applicant elected "antibody" as species of ligand and second ligand. Two subsequent Office Actions (mailed December 18, 2002 and September 5, 2003, respectively) levied §§ 102 and 103 rejections in which the Examiner discussed cited references describing cell-based assays involving antibodies. Therefore, Applicant prosecuted this case with the assumption that the embodiment whereby the ligand is an antibody (i.e., elected species) had been subject to a search. However, to Applicant's surprise, during a phone conversation with the undersigned on April 28, 2004, the Examiner stated that such search had not been done, and that further search and consideration of the claims, as amended in the 11/05/03 Response, was therefore necessary. Accordingly, the Request for Continued Examination submitted concurrently herewith is being filed to provide the Examiner with an opportunity to properly examine the claims.

Claims 57-81 and 83-104 are currently pending in the subject application. Claim 84 is withdrawn from consideration by the Examiner under 37 C.F.R. § 1.142(b) as being drawn to a non-elected invention. Claims 57-81, 83 and 85-103 are currently under consideration and stand rejected under 35 U.S.C. §§102, 103 and 112 based on a number of positions laid out in detail in the 9/5/03 Final Office Action. Applicant respectfully disagrees with the conclusions set forth in that office action. However, in order to expedite prosecution of a portion of their invention of particular current interest, Applicant has presented a set of more narrowly focused amended

claims on pages 2-16 of this paper. Specifically, Applicant has canceled claims 61 and 62, and has amended claims 57-59, 63-65 and 81, in part to introduce the subject matter of now canceled claims 61 and 62. All the other claims remain unchanged. Below we address each of the rejections stated in the Office Action as if it were applied to the newly amended claims.

Applicant reiterates that the deletion of any claims and any other loss of claimed subject matter is being made solely to expedite prosecution of the subject matter now claimed, rather than in acquiescence to any positions taken by the Examiner. In fact, Applicant is *not* acquiescing to any of those positions and is submitting this amendment without prejudice to the subsequent prosecution of claims to some or all of the subject matter which might be lost by virtue of this paper. Applicant explicitly reserves the right to pursue this subject matter in divisional or continuation applications.

Amendments to Claims

Claims 57-59, 64, 65 and 81, as amended, recite an antibody. Support for this amendment can be found, for example, in (now canceled) claims 61 and 62, which recited that the ligand could be an antibody. Accordingly, the amendment replacing the term "ligand" with "antibody" in claims 57-59, 64, 65 and 81 does not introduce new matter.

Without conceding the correctness of the Examiner's position with respect to possible § 112, 2nd paragraph issues regarding the language "antibody-component", but solely to expedite prosecution, Applicant has amended claim 57 to recite "association between the antibody and the component."

Claim 58 has been amended to replace "wherein seconds are thirds" with "wherein the second antibody is a third antibody". In doing so, Applicant merely adopted language that the Examiner had suggested, namely, replace the language "wherein seconds are thirds" with "wherein the second ligand is a third ligand" (See paper 30 mailed September 5, 2003, page 4, section 12, last sentence). In addition, Applicant incorporated the limitation of (now canceled) claim 62 that the ligand is an antibody, thereby introducing the language "wherein the second antibody is a third antibody". No new matter is being introduced with these amendments.

Claim 63 has been amended to correct claim dependency, rendered necessary by cancellation of claims 61 and 62.

In addition, claim 81 has been amended to change claim dependency and to incorporate the limitations of claims 76 and 79 from which it depends. Specifically, claim 76 recites that the intracellular biological or chemical process may be a covalent modification of an intracellular component, and claim 79 recites that the covalent modification may be a post-translational event and the intracellular component a protein. Therefore, the language "the intracellular biological or chemical process is a post-translational modification of a protein, and the antibody interacts with the post-translationally modified protein" found in currently amended claim 81 does not present new matter.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claim 62 under 35 U.S.C. § 112, second paragraph and states that claim 62 recites a limitation on a "third ligand" which the Examiner alleges does not have antecedent basis in claim 58 from which it depends. Without conceding the correctness of the Examiner's position, but solely in an effort to expedite prosecution, Applicant has amended claim 58 to change the language "*wherein seconds are thirds*" to "*wherein the second antibody is a third antibody*", as suggested by the Examiner in the Office Action mailed September 9, 2003. Therefore, the stated rejection is now moot.

In view of the amendments detailed above, Applicant asserts that the claims, as amended, particularly point out and distinctly claim the invention, and respectfully requests that the rejections under 35 U.S.C. § 112, second paragraph be withdrawn.

Rejection under 35 U.S.C. § 102(b)

Claims 57, 59-61, 64, 66, 67, 69, 71-74, 76-79, 81-83, 85-88, 102-103 and 104 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Photiou *et al.* (European Journal of Cancer, 33(3):463-470, March 1997). Specifically, the Examiner states that Photiou *et al.* disclose a cell-based assay in high-throughput format, citing second column lines 13-21 on page 464.

Applicant reiterates and maintains that the Photiou *et al.* reference *did not* anticipate the claims prior to the 11/5/03 amendment (*i.e.,* claims reciting a "ligand"), and still *does not* anticipate the instant claims (*i.e.,* claims reciting an "antibody"). Applicant notes that the section of the Photiou *et al.* reference that the Examiner is referring to relates to a cell growth

inhibition assay whereby "cells were seeded at 3000 cells/well/100 µl in 96-well flat-bottomed plates". Applicant fails to find *any* description in that section, or anywhere in the Photiou *et al.* reference, of a high-throughput assay comprising steps of introducing into each of a plurality of reaction vessels (i) a plurality of cells, (ii) one or more test compounds whose effect on an intracellular biological or chemical process is to be evaluated, and (iii) *an antibody that associates intracellularly with a biological component whose presence or amount reveals the effect of a given test compound on the biological or chemical process*; and (iv) *assaying for association between the antibody and the component in the reaction vessels*; wherein the plurality of reaction vessels comprises at least 96 reaction vessels. If Applicant is mistaken, the Examiner is invited to point out where, in the section entitled "Isobologram method" on page 464, second column, lines 13-21, is found any reference to an antibody that associates intracellularly with a biological component or a step of assaying for association between the antibody and the component in the reaction vessels (*e.g.*, wells). Applicant contends that, absent an explicit description of the presently claimed invention in the Photiou *et al.* reference (*i.e.*, including ***all*** the claim limitations), the cited reference cannot be held to anticipate the instant claims.

In summary, the present Examiner, and the Examiner previously assigned to the case, have failed to identify *any* explicit description of the presently claimed invention in the Photiou *et al.* reference (*i.e.*, including ***all*** the claim limitations). Therefore, the cited reference cannot anticipate the instant claims. Applicant asserts that the rejection under 35 U.S.C. § 102(b) over the Photiou *et al.* reference is improper, and hereby respectfully requests that the stated rejection be withdrawn.

Rejection under 35 U.S.C. § 102(e)

Claims 57-81, 83 and 85-104 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Taylor (U.S. Patent No.: 6,103,479). Specifically, the Examiner states that Taylor discloses a high-throughput method for screening physiological response of cells to biologically active compounds, said method comprising preparing an array of cells, contacting the array of cells with a fluid delivery system to enable reagent delivery to the array of cells, conducting high-throughput screening by acquiring an image of the entire array of cells to detect signal from all wells at once to identify cells that exhibit a response, converting the signal into digital data and

utilizing the digital data to determine the distribution, environment or activity of cells, citing for example column 13, lines 37-56 and Example 2 columns 19-20.

Taylor's screening method differs from Applicant's claimed invention at least in that it uses luminescent reporter molecules as means of detection, not *an antibody* which, after introduction in the reaction vessels (*e.g.*, wells), *associates intracellularly with a biological component whose presence or amount reveals the effect of a given test compound on the biological or chemical process*. [See, for example, column 13 lines 37-56 and Example 2 columns 19-20 (cited by the Examiner), as well as the background section which focuses on the use of reporter molecules as detection methods (*e.g.*, in assays) - column 4 lines 56-67 and column 5 lines 1-67]. In other words, the cells are modified (*e.g.*, genetically engineered) so that a pre-determined indicator (*e.g.*, a fluorescent protein) is expressed in the cells under prescribed conditions. As evidenced throughout Taylor's disclosure (for example, column 6 lines 61-62, column 13 lines 37-56, Taylor's method comprises means to detect, record and analyze the luminescent signals from the luminescent reporter molecules present in the cells. Accordingly, the "reporter molecule" which is already present in the cells prior to running the screen (*i.e.*, "internal" indicator), is used to identify cells that exhibit a response. Moreover, Taylor's method does not comprise a step of assaying for association between the antibody and the component in the reaction vessels.

Furthermore, Taylor's method comprises a step of attaching the cells to a non-uniformly chemically modified micro-patterned array (see, for example, column 8, lines 28-32 and claim 1 (d)). As a result, as detailed in column 6, lines 24-27, in Taylor's method, the *delivery of cells to the "wells" is based on specific binding* (see, also, column 12 lines 1-9).

In summary, Applicant's claimed invention does not require a step of attaching the cells to a non-uniformly chemically modified micro-patterned array, nor does it use reporter molecules as means of detection. Moreover, Taylor does not teach use of an antibody that associates intracellularly with a biological component whose presence or amount reveals the effect of a given test compound on the biological or chemical process. In light of the above remarks, the Taylor reference cannot anticipate the claimed invention. Applicant respectfully requests that the stated rejection be withdrawn.

Rejection under 35 U.S.C. § 103

Although not explicitly referred to in the Advisory Actions mailed December 24, 2003 and March 10, 2004, Applicant addresses below the § 103 rejection levied in the final rejection mailed 9/5/03 in an effort to make perfectly clear that the stated rejection is *de facto* improper.

Claims 89-101 are rejected under 35 U.S.C. § 103(a) as being unpatentable over any one or more of Walsh (U.S. patent 5,990,092), Photiou *et al.* (European Journal of Cancer, 33(3):463-470, March 1997), Juan *et al.* (Experimental Cell Research, 239:104-110, February 1988), Claycomb (U.S. patent 6,316,207 B1; PCT published May 1998) and the Final Conference Program of LabAutomation '98 in San Diego, CA January 17-21, 1998, pages 99, 100, 124, 129 and 212. However, the Examiner concedes that the cited references do not explicitly teach test compounds from a combinatorial library, the release of test compounds from a solid support, *or various capacities and densities of wells in well plates.*

Applicant respectfully disagrees with the conclusions of the Examiner. Specifically, the legal standard for establishing a *prima facie* case of obviousness requires that three basic criteria be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one skilled in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success in the modification or in the combination; and (3) the prior art reference must teach all the claim limitations. All three requirements must be met to establish a *prima facie* case of obviousness. In addition, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure (MPEP 706.02(j)).

Applicant maintains that the Examiner has failed to establish a prima facie case of obviousness because at least one the above requirements is not met. To provide a clear record, Applicant points out that the arguments set forth below (and in the 11/5/03 Response) refer to the amended claims (*i.e.*, claims including the "antibody" limitation). However, the arguments are equally valid for the claims presented prior to the amendment (*i.e.*, claims reciting a "ligand"), as detailed on pages 13-15 of Applicant's Response filed May 19, 2003. The arguments presented in the present paper (and in the 11/5/03 Response) do not infer, nor should they be construed to mean, that the introduction of the "antibody" limitation changed anything to the impropriety of the § 103 rejection levied in the 9/5/03 final rejection

A. ***Motivation to combine***

Applicant asserts that none of the Walsh, Photiou *et al.*, Juan *et al.*, Claycomb references teach a *high-throughput* assay comprising steps of introducing into each of a plurality of reaction vessels (i) a plurality of cells, (ii) one or more test compounds whose effect on an intracellular biological or chemical process is to be evaluated, and (iii) an antibody that associates intracellularly with a biological component whose presence or amount reveals the effect of a given test compound on the biological or chemical process; and (iv) assaying for association between the antibody and the component in the reaction vessels; *wherein the plurality of reaction vessels comprises at least 96 reaction vessels*.

Specifically, Claycomb teaches a cell proliferation assay using BrdU labeling, where the cells are plated on coverslips in *12-well plates* in *1 ml* of suitable medium.

Photiou *et al.* teach an indirect immunofluorescence assay where the cells are plated on coverslips in *24-well plates*. Applicant reiterates that the assay involving 96-well plates in the section entitled "Isobologram method" on page 464, column 2, lines 13-21 of the Photiou *et al.* reference differs from the high throughput method of the presently claimed invention at least in that it lacks any reference to (i) an antibody that is introduced in the plurality of vessels, and bind intracellularly to a biological component of interest, or (ii) a step of assaying for association between the antibody and the component in the reaction vessels (*e.g.*, wells).

Juan *et al.* disclose an immunocytochemical assay for pRb phosphorylation. However the reference does not provide specific teaching or suggestion to conduct the assay in high throughput format.

Similarly, the Walsh reference does not specifically teach a high-throughput screening method (*e.g.*, number of reaction vessels $\geq$ 96) according to the claimed invention. In fact, the *in vitro* assay of Example 4 in the Walsh reference (column 28 lines 47-57) which the Examiner refers to, describes that the "cells are fixed onto *the tissue culture dish* and dried overnight at 37°C and immunostained..." Thus, the method disclosed in the Walsh reference only utilizes *one* reaction vessel.

In summary, none of the Walsh, Photiou *et al.*, Juan *et al.*, Claycomb references teach or suggest that the cell-based assays in question can be carried out in high-throughput format (*e.g.*, with 96 or higher reaction vessels) nor do they provide any teaching or suggestion as to how this might be accomplished.

With respect to the "Final Conference Program of LabAutomation '98" reference, while the reference provides examples of the use of 96-, 384-, 1536- and 10,000-well plates in one enzymatic fluorescent kinetic assay (see page 100), Applicant cannot find any specific teaching or suggestion in that reference that these high density plates (*i.e.*, 96-, 384-, 1536- and 10,000-well plates) can be used in cell-based assays such as those described in the Walsh, Photiou *et al.*, Juan *et al.*, Claycomb references. Applicant invites the Examiner to specifically point out where in the "Final Conference Program of LabAutomation '98" reference may be found specific teaching or suggestion that the aforementioned high density plates may be used in a high-throughput assay comprising steps of introducing into each of a plurality of reaction vessels (i) a plurality of cells, (ii) one or more test compounds whose effect on an intracellular biological or chemical process is to be evaluated, and (iii) an antibody that associates intracellularly with a biological component whose presence or amount reveals the effect of a given test compound on the biological or chemical process; and (iv) assaying for association between the antibody and the component in the reaction vessels.

In summary, none of the cited references provide any specific teaching or suggestion to modify or combine the teachings of "Final Conference Program of LabAutomation '98" reference and any one or more of the Walsh, Photiou *et al.*, Juan *et al.*, Claycomb references to achieve the claimed invention. Absent any such teaching or suggestion in any of the cited references, the stated combination of references cannot be held to render obvious the claimed invention.

B. ***Reasonable expectation of success***

Applicant contends that the report of the mere existence of high-density plates (*e.g.*, 96-, 384-, 1536- and 10,000-well plates) in the "Final Conference Program of LabAutomation '98" reference does not, and cannot be held to, imply or suggest that they can *successfully* be used for any cell-based assay known in the art at the time (*e.g.*, cell-based assays disclosed for example in the Walsh, Photiou *et al.*, Juan *et al.* and/or Claycomb references). Applicant reiterates that the example described on page 159 of the "Final Conference Program of LabAutomation '98" reference supports this position. Specifically, despite the existence of 96-, 384-, 1536- and 10,000-well plates at the time, Henderson *et al.* were only able to develop a *24-well* system for the cell-based assay in question. This reinforces the statement on page 159 first paragraph that "*some cell-based assays remain difficult to automate.*" Therefore, even if there were suggestion

or teaching in any one of the cited references to combine the teachings of the "Final Conference Program of LabAutomation '98" reference with the teachings of any one or more of the Walsh, Photiou *et al.*, Juan *et al.* and/or Claycomb references, there would be no reasonable expectation of success in the combination.

The Examiner invokes the reference to "significant advantages in both cost and speed" found on page 99 of the "Final Conference Program of LabAutomation '98" reference to support a finding of reasonable expectation of success. Applicant respectfully submits that "advantages" related to speed and cost have little to do with expectation of success. As discussed above, the mere existence of high-density plates does not imply or suggest that they can *successfully* be used for any cell-based assay known in the art at the time. In fact, the "Final Conference Program of LabAutomation '98" reference specifically teaches that automation of cell-based assays can be difficult (see, for example, page 159). Therefore, the Examiner's assertion that the skilled practitioner would have been motivated to combine the cited references because there is reasonable expectation of success is simply unfounded.

Accordingly, Applicant maintains that the Examiner has applied an improper "obvious to try" rationale because there is no reasonable expectation of success in the combination of the cited references.

In summary, Applicant has clearly demonstrated that the cited combination of references does not meet the legal standard for establishing a *prima facie* case of obviousness. Specifically, there is no teaching or suggestion in any of the cited references to modify or combine the teachings of any one or more of the Walsh, Photiou *et al.*, Juan *et al.*, and/or Claycomb references and the teachings of the Final Conference Program of LabAutomation '98 reference to achieve the claimed invention. In addition, Applicant has established that there is no reasonable expectation of success in the combination. Accordingly, the rejection under 35 U.S.C. § 103(a) levied in the 9/5/03 final rejection is improper.

CONCLUSION

Based on the Remarks presented above, Applicant submits that the claims, as amended herein, are allowable over the art of record. The claims are fully supported by the specification and the amendments presented in the present paper do not present new matter. The patent should issue. A Notice to that effect is respectfully requested.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those which may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required for consideration of this paper (including fees for net addition of claims) are authorized to be charged to our Deposit Account No. 03-1721.

Respectfully submitted

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Nadège M. Lagneau, Ph.D.
Agent for Applicant
Registration. No. 51,908

PATENT GROUP
CHOATE, HALL, & STEWART
Exchange Place
53 State Street
Boston MA 02109
Telephone: 617-248-5000
Facsimile: 617-248-4000